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| 10/521,454      | 11/29/2005  | Ichiro Hirao         | 0230-0222PUS1       | 8799             |

2292 7590 05/29/2009  
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| EXAMINER |
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EPPS -SMITH, JANET L

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| ART UNIT | PAPER NUMBER |
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1633

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| NOTIFICATION DATE | DELIVERY MODE |
|-------------------|---------------|

05/29/2009

ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

|                              |  |                                     |  |
|------------------------------|--|-------------------------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b><br>10/521,454   | <b>Applicant(s)</b><br>HIRAO ET AL. |  |
|                              | <b>Examiner</b><br>Janet L. Epps-Smith | <b>Art Unit</b><br>1633             |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 09 March 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 2-15 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 2-15 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 May 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03-09-2009 has been entered.

2. Claims 2-15 are presently pending for examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

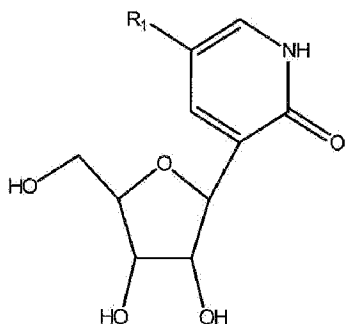
### ***Response to Amendments/Arguments***

#### ***Claim Rejections - 35 USC § 103***

4. Claims 2-9, and 11-14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Froehler et al. (US Patent NO. 6447998 or 6495672 or US application number 20030120065), in view of Ohtsuki et al. and Guo et al. (1998; Applicant's IDS filed), for the reasons of record.

5. Applicant's arguments filed 03/09/2009 have been fully considered but they are not persuasive, additionally the Declaration filed under 37 CFR 1.132 filed 03/09/2009 is insufficient to overcome the rejection of claims 2-9 and 11-14 based upon 103(a) as set forth in the last Office action because: Applicant's arguments and the arguments

presented in the Declaration are both centered upon the characterization of the claimed invention as being drawn to the following structure.



(see Applicant's Reply page 13, and the Declaration page 3)

However, this structure is not recited in the any of the pending claims. There is no requirement that the 5-substituted-2-pyridone base form a linkage with the  $\beta$ -D-ribofuranosyl sugar at the 3-position. Therefore, Applicant's arguments and the showing in the Declaration are not commensurate in scope with the claimed invention. Moreover, Applicant's have not provided sufficient evidence that the skilled artisan seeking alternative 5-substituted-2-pyridone derivatives, and having knowledge of synthetic pathways disclosed Froehler et al., Ohtsuki et al., and Guo et al. would not have been able to substitute the 5-position with a bromine, or iodine residue, with the expectation of producing a compound of similar function and utility.

Contrary to Applicant's assertions, simply because the exact synthetic pathway for the production of the compounds of the instant invention are not disclosed in the cited references is not sufficient to say that the cited references are not enabling. As stated in the prior Office Action, one of ordinary skill in the art would have been motivated to modify the teachings of Froehler et al. to design the molecules of the instant invention, by modifying the pyrimidine analogue to comprise a 2-keto group

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since it was known in the prior art at the time of filing that such groups are necessary for interaction with DNA polymerase. One of ordinary skill in the art would have had a reasonable expectation of success in making this modification since the prior art teaches the ordinary skilled artisan how to make pyrimidine nucleosides analogues comprising a 5-substituent (see Froehler et al.) and a 2-keto group (Ohtsuki et al.), and further teaches how to incorporate these analogues into nucleic acid (see Ohtsuki et al.)

Moreover, with respect to claims 4 and 12 that are limited to wherein the 5-position of the base is substituted with an iodine or biotin derivative, it is noted that the cited prior art describes nucleoside structures comprising 5-substitutions including wherein the substituents is hydrogen, methyl, and alkynyl groups. The instantly claimed compounds, are considered to be obvious analogues of the prior art compounds due to the close structural similarity to the prior art compounds, and to the extent that there does not appear to be a critical role for the substituents of the 5'-position. See MPEP § 2144.09 which states:

**2144.09 Close Structural Similarity Between Chemical Compounds (Homologs, Analogues, Isomers)**

**REJECTION BASED ON CLOSE STRUCTURAL SIMILARITY IS FOUNDED ON THE EXPECTATION THAT COMPOUNDS SIMILAR IN STRUCTURE WILL HAVE SIMILAR PROPERTIES**

A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991) (discussed below and in MPEP § 2144) for an extensive review of the case law pertaining to obviousness based on

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close structural similarity of chemical compounds. See also MPEP § 2144.08, paragraph II.A.4.(c).

**HOMOLOGY AND ISOMERISM ARE FACTS WHICH MUST BE CONSIDERED WITH ALL OTHER RELEVANT FACTS IN DETERMINING OBVIOUSNESS**

Compounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH<sub>2</sub>- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See also In re May, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (stereoisomers prima facie obvious).

Therefore, the invention as a whole would have been prima facie obvious over the teachings of Froehler et al. in view of Guo et al. and Ohtsuki et al.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2-15 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter).

8. Applicant's arguments filed 03/09/2009 have been fully considered but they are not persuasive. Applicants traversed the instant rejection on the following grounds:

9. "[A]lthough Applicants disagree, in order to advance prosecution, claims 2, 3, 5, 11, and 13- 15 have been amended, without prejudice or disclaimer, to further clarify

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and define the invention. Specifically, Applicants have amended the claims wherein the 5-position of the base is not substituted with a substituent that is an alkenyl group, an alkynyl group or an amino group.

10. However, contrary to Applicant's assertions, Applicant's amendment to the claims does not change the scope of the claims to the extent that they still encompass the following, wherein the 5-position of the 5-substituted-2-oxo-(1H)-pyridin-3-yl group is substituted with:

**"4) biotin, dichloroacetyl group, fluorescein, 6-carboxyfluorescein, tetramethyl-6-carboxyrhodamine, or derivatives thereof introduced via a linker selected from an aminoalkyl group, an aminoalkenyl group and an aminoalkynyl group."**

Applicant's amendment does not remedy the observation that the specification as filed fails to support derivatives of dichloroacetyl group, fluorescein, 6-carboxyfluorescein, tetramethyl-6 carboxyrhodamine introduced at the 5- position of the nucleotide or nucleoside of the invention via a linker selected from an "aminoalkyl group, an aminoalkenyl group and an aminoalkynyl group."

Applicant's amendment is therefore considered to add new matter to the scope of the claimed invention, since the full scope of the claimed invention does not find support in the specification as originally filed.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 2-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-15 appear to claim a Markush group without the proper use of the Markush format. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. The metes and bounds of this Markush group is indefinite because it is unclear if the members of this group are mutually exclusive. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See *Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925). In the instant case, the instant claims recite wherein the 5-position is substituted from a group which recites biotin in item #2 and a derivative thereof, and further recites biotin or a derivative thereof introduced via a linker selected from an aminoalkyl group, an amino alkenyl group and an aminoalkynyl group. The instant claims are indefinite since (1) it includes the following broad terms: "biotin, dichloroacetyl, fluorescein, 6-carboxyfluorescein, tetramethyl-6-carboxyrhodamine, and derivatives thereof;" and further recites (2) biotin, dichloroacetyl, fluorescein, 6-carboxyfluorescein, tetramethyl-6-carboxyrhodamine, and derivatives thereof introduced via a linker selected from an aminoalkyl group, an amino alkenyl group and an aminoalkynyl group, a narrower limitation.

It is clear that the members of the Markush group, for example, wherein "biotin" is recited twice, does not set forth a non-mutually exclusive group.



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1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Smith whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Epps-Smith/

Primary Examiner, Art Unit 1633